AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application.

LISTING OF CLAIMS

Claims 1-44 (cancelled)

Claim 45 (currently amended): A method for identifying a compound which reduces the activity or level of a gene product required for proliferation of a microorganism, said method comprising the steps of:

(a) ~~reducing the activity or amount of a gene product in a cell by~~ expressing a sub-lethal level of an antisense nucleic acid complementary to a nucleic acid ~~encoding~~ in a microbial cell, wherein said nucleic acid encodes a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60, thereby producing a sensitized microbial cell;

(b) contacting said sensitized microbial cell with a compound; and

(c) determining whether said compound inhibits the growth of said sensitized microbial cell.

Claim 46 (currently amended): The method of Claim 45, wherein said determining step comprises determining whether said compound inhibits the growth of said sensitized microbial cell to a greater extent than said compound inhibits the growth of a nonsensitized cell.

Claim 47 (currently amended): The method of Claim 45, wherein said microbial cell is selected from the group consisting of bacterial cells~~, fungal cells, plant cells, and animal cells~~ and fungal cells.

Claim 48 (currently amended): The method of Claim 45, wherein said microbial cell is a Gram negative bacterium.

Claim 49 (currently amended): The method of Claim 45, wherein said microbial cell is an *E. coli* cell.

Claim 50 (currently amended): The method of Claim 45, wherein said microbial cell is from an organism selected from the group consisting of *Aspergillus fumigatus, Bacillus anthracis, Burkholderia cepacia, Campylobacter jejuni, Candida albicans, Candida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida*

guilliermondii, Candida krusei, Candida kefyr (also called Candida pseudotropicalis), Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Clostridium difficile, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Listeria monocytogenes, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, ~~Klebsiella pneumoniae~~, ~~Listeria monocytogenes~~, Moxarella catarrhalis, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, ~~Pseudomonas aeruginosa~~, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, Yersinia pestis and any species falling within the genera of any of the above species.

Claim 51 (original): The method of Claim 45, wherein said antisense nucleic acid is transcribed from an inducible promoter.

Claim 52 (currently amended): The method of claim 51, further comprising the step of contacting said microbial cell with an inducer in a concentration which induces said antisense nucleic acid to a sub-lethal level.

Claim 53 (original): The method of Claim 45, wherein growth inhibition is measured by monitoring optical density of a culture growth solution.

Claim 54 (original): The method of Claim 45, wherein said gene product is a polypeptide.

Claim 55 (currently amended): The method of Claim 54, wherein said polypeptide comprises ~~a~~ an amino acid sequence ~~selected from the group consisting~~ of SEQ ID NO: 413.

Claim 56 (currently amended): The method of Claim 45, wherein said gene product is ~~an~~ a RNA.

Claims 57-127 (cancelled)

Claim 128 (withdrawn): A method for manufacturing an antibiotic comprising the steps of manufacturing a compound which has been determined to inhibit the growth of a sensitized cell using the method of Claim 45.

Claims 129-131 (cancelled)

Claim 132 (previously added) A method for manufacturing an antibiotic comprising the steps of manufacturing a compound which has been determined to inhibit the growth of a sensitized cell using the method of Claim 46.

Claim 133 (new) A method for identifying a compound which reduces the activity or level of a gene product required for proliferation of a microorganism, said method comprising the steps of:

(a) expressing a sub-lethal level of an antisense nucleic acid complementary to a nucleic acid in a microbial cell, wherein said nucleic acid encodes a gene product having at least 70% amino acid identity to a gene product comprising the amino acid sequence of SEQ ID NO: 413, thereby producing a sensitized microbial cell;

(b) contacting said sensitized microbial cell with a compound; and

(c) determining whether said compound inhibits the growth of said sensitized microbial cell.

Claim 134 (new) The method of Claim 45, wherein said microbial cell is a Gram positive bacterium.

REMARKS

Claims 1-44, 57-127, and 129-131 have been cancelled. Claims 133 and 134 have been added. Claims 45-50, 52, 55 and 56 have been amended. Pending claim 132, which was added in response to the first Office Action but which was neither withdrawn nor examined in the Final Office Action, is re-presented for examination. Claims 45-56 and 133 are currently presented for examination; however, as discussed further below, Applicants additionally request that Claims 128 and 132 be examined.

No new matter has been added to the application. Claims 45-50 and 52 have been amended to add the term "microbial" prior to the term "cell." Claim 45 has also been amended to remove the phrase "reducing the activity or amount of a gene product in a cell by." Support for these amendments can be found throughout the specification. Support for new claim 133 can be found at page 30, line 27 to page 32, line 20. Claims 55 and 56 have been amended to correct minor informalities.

Telephonic Interview

Applicants wish to thank the Examiner for the his instructive comments during the telephonic interview of May 12, 2003. As agreed in that interview, in addition to this response to the Final Office Action, Applicants are providing herewith a Declaration by the Inventor under 37 C.F.R. § 1.132.

Overview

Before addressing each item in the Final Office Action, Applicants would like to provide a brief background regarding the discovery of the nucleic acids and polypeptides recited in the claims in order to provide context for the Examiner's review of the accompanying Declaration.

Using the antisense method described in the section entitled Examples (pages 37-40) of the instant application, Applicants have discovered a number of proliferation-required genes, one of which was *yid*C, and a number of antisense nucleic acids which inhibit proliferation, one of which was SEQ ID NO: 60. The described antisense method utilizes sheared genomic DNA from a host microorganism to generate a library containing both sense and antisense fragments of the host's genomic DNA. In one version of this method, the genomic fragments are cloned under the control of an inducible promoter (e.g. the *lac* promoter) into a plasmid which replicates in the

host cell. The host cells are transformed with the library of plasmids which comprise the genomic fragments in either the sense or antisense orientation. Expression of the cloned fragments is then induced from the inducible promoter, such as the *lac* promoter, by adding an inducer, such as IPTG. The growth of transformed cells which have been induced to express a genomic fragment from the plasmid is compared to the growth of transformed cells which have not been induced (control cells). Induced cells that have a reduced growth rate or exhibit no growth as compared to the control cells are those which express a portion of an essential gene in an antisense orientation. Sequencing the proliferation-inhibiting genomic fragment reveals the sequence of an antisense nucleic acid that inhibits cellular proliferation by reducing the activity or level of a product of the proliferation-required gene (for example reducing the level of an mRNA or the activity of a polypeptide that is encoded by the identified proliferation-required gene). In addition, because the inhibitory antisense nucleic acid is complementary to at least a portion of the proliferation-required gene, the sequence of the proliferation-required gene can be readily obtained.

Using the above-described methods, Applicants were first to discover that the product of the *yid*C gene is required for proliferation. In particular, Applicants found that antisense nucleic acids complementary to at least a portion of the *yid*C gene, including the antisense nucleic acid of SEQ ID NO: 60, inhibits the proliferation of *E. coli.* Using known *E. coli* genomic sequence information, Applicants found that the antisense nucleic acid of SEQ ID NO: 60 is complementary to at least a portion of the *yid*C gene (SEQ ID NO: 220), which encodes the YidC polypeptide (SEQ ID NO: 413). The inhibition of proliferation results from the antisense-mediated reduction in the level the proliferation-required product of the *yid*C gene, such as the *yid*C mRNA or the YidC polypeptide which is translated from the *yid*C mRNA. This reduction in the level of proliferation-required gene product permits one to screen compounds to determine whether any of the compounds further act on the proliferation-required gene product to further inhibit cellular proliferation. Thus, such expression of an antisense nucleic acid that is complementary to at least a portion of the *yid*C gene causes the cell to become sensitized to compounds to which it would not normally be sensitive. As such, Applicants' results demonstrated that antisense nucleic acids, such as SEQ ID NO: 60, which inhibit the expression of proliferation-required gene products, such as the YidC polypeptide, can be used to sensitize cells for use in assays to identify potential antimicrobial compounds.

Claim Objections

The Examiner objects to Claims 55 and 56 due to informalities. Each of these claims have been amended as recommended by the Examiner to correct the cited informalities. Accordingly, Applicants respectfully request that the Examiner withdraw his objections to Claims 55 and 56.

Rejection of Claims 45-56 Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejects Claims 45-56 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. With respect to Claim 45, the Examiner asserts that it is unclear whether "a gene product in a cell" is the same as "a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60." Because Claims 46-56 are dependent on Claim 45, they are also rejected.

In order to expedite allowance of the instant application, Applicants have presently amended Claim 45 to remove the phrase "reducing the activity or amount of a gene product in a cell by." This amendment effectively deletes all occurrences of the phrase "a gene product in a cell" from Claim 45. Accordingly, Applicants believe that this claim amendment overcomes the Examiner's rejection.

In view of the above claim amendments and remarks, Applicants respectfully request that the Examiner withdraw his rejection of Claims 45-56 under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 45-56 Under 35 U.S.C. § 112, First Paragraph - Written Description

The Examiner rejects Claims 45-56 under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the invention was possessed when the application was filed.

Applicants maintain that the requirements of 35 U.S.C. § 112, first paragraph are satisfied with respect to the above-rejected claims. Claims 45-56 each recite a method for identifying a compound which reduces the activity or level of a gene product required for proliferation of a microorganism by expressing a sub-lethal level of an antisense nucleic acid complementary to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid

comprising a nucleotide sequence of SEQ ID NO: 60. To determine the necessary written description for such claims, the Examiner is invited to review Example number 15 of the Written Description Training Materials (available at the USPTO website) which is based on and in accordance with the Written Description Guidelines (66 FR 1099, January 5, 2001) promulgated by the USPTO. Example 15 of the Training Materials illustrates a case where the written description of an application supports a claim to a genus of antisense molecules that inhibit the production of human growth hormone (HGH). In this example, the applicant has disclosed SEQ ID NO: 1 (HGH) and has stated that the invention includes antisense oligonucleotides complementary to SEQ ID NO: 1. The applicant has also described a method of screening for antisense molecules. The example goes on to state that it well known in the art that a full-length antisense nucleic acid has inhibitory activity as do fragments of the full-length antisense nucleic acid provided that the they match accessible regions of the target nucleic acid. In consideration of the description provided by the applicant in Example 15, the Training Materials go on to state that, in view of the level of knowledge in the art, a skilled artisan would recognize that the applicant possessed the genus embraced by a claim drawn to all antisense nucleic acids complementary to SEQ ID NO: 1 which inhibit HGH production, because the applicant has disclosed a full-length HGH sequence, a functional characteristic of the antisense nucleic acids (the inhibitory function) and a method of screening for such antisense nucleic acids. Accordingly, the Training Materials state that the claim in Example 15 is adequately described.

Like the applicants in Example 15 of the training materials, Applicants here have described the full-length *yid*C coding sequence (SEQ ID NO: 220) and its complement. In addition to the full-length antisense, Applicants have described an antisense fragment (SEQ ID NO: 60) which is complementary to at least a portion of the *yid*C gene and which inhibits the expression of the *yid*C gene product thereby inhibiting cellular proliferation. (See Examples 1-3 and Tables 1 and 2 as well as the accompanying Declaration). Applicants also describe a method of screening for additional proliferation-inhibiting antisense nucleic acids that are complementary to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60. In particular, Applicants describe a method for introducing antisense nucleic acids into a cell, determining the extent of the inhibition of cellular proliferation that results (see Example 1 at page 39, line 23, to page 40, line 4) and then isolating and characterizing those antisense nucleic acids which have proliferation-inhibiting

activity (see Examples 1 and 2 at page 40, lines 6 to 19). Applicants also describe numerous antisense nucleic acids which are complementary to the *yid*C gene and which can be screened by the above-mentioned method for their ability to inhibit cellular proliferation by inhibiting the expression of the *yid*C gene product. Such antisense nucleic acids are described at page 30, line 11 to page 31, line 8, and include, nucleic acids which comprise at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400 or 500 consecutive nucleotides of a sequence complementary to SEQ ID NO: 220 (*yid*C) or a sequence complementary to a nucleotide sequence encoding a protein of SEQ ID NO: 413 (YidC) (see page 30, line 11 to page 31, line 8). Additionally, it is readily appreciated within the art that antisense nucleic acid fragments of any size which correspond to at least a portion of the *yid*C gene can be assayed for the ability to inhibit cellular proliferation using the methods described herein or methods known to those of ordinary skill in the art.

In view of the above remarks, Applicants submit that the instant specification provides adequate written description for Claims 45-56. Accordingly, Applicants respectfully request that the Examiner withdraw his rejection of claims 45-56 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 45-56 Under 35 U.S.C. § 112, First Paragraph - Enablement

The Examiner rejects Claims 45-56 under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to enable a skilled artisan to make and/or use the claimed invention. In particular, the Examiner asserts that Applicants have provided no evidence that a nucleic acid comprising the nucleotide sequence of SEQ ID NO: 60 can function as an antisense nucleic acid that inhibits cellular proliferation. The Examiner also asserts that Applicants provide no guidance or working examples for producing a sensitized cell by reducing the activity of amount of a gene product in a cell by expressing a sub-lethal level an of antisense nucleic acid complementary to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60. The Examiner goes on to assert that whether cells would become sensitized in response to the expression of antisense nucleic acids is unpredictable. Finally, the Examiner asserts that significant trial and error experimentation is required to determine whether an antisense nucleic acid can function *in vivo*. Each of these issues are addressed in turn below.

With respect to the first aspect of the Examiner's enablement rejection, Applicants respectfully disagree that the instant specification lacks sufficient support which shows that SEQ ID NO: 60 functions as a proliferation-inhibiting antisense molecule. Applicants would like to draw the Examiner's attention to working Examples 1 and 2, which describe methods for identifying proliferation-inhibiting antisense nucleic acids which are complementary to proliferation-required genes and gene products, as well as the results of these methods which are summarized in Tables 1 and 2. Table 1 lists the SEQ ID NO of the antisense nucleic acids that were shown to inhibit cell proliferation as well as the essential gene to which the inhibitory antisense nucleic acid is complementary. Table 1 on page 42 (last line) indicates that SEQ ID NO: 60 is an antisense nucleic acid which inhibits proliferation of *E. coli* and which is complementary to the gene encoding the YidC protein. Table 2 provides the SEQ ID NO for the *yid*C coding strand and YidC protein (SEQ ID NOs: 220 and 413, respectively). Applicants have further provided a Declaration by one of the inventors, Dr. R. Allyn Forsyth, which shows that prior to the filing of the instant patent application, SEQ ID NO: 60 was identified as an antisense nucleic acid complementary to at least a portion of the *yid*C gene which effectively inhibits the proliferation of *E. coli*.

In view of the working examples in the specification and the information provided in the declaration, Applicants maintain that they have provided substantial support showing that SEQ ID NO: 60 functions as a proliferation-inhibiting antisense molecule which can be used to sensitize cells by inhibiting the activity or level of a *yid*C gene product.

With respect to the next aspect of the enablement rejection, it is alleged that Applicants provide no guidance or working examples that would enable a skilled artisan to produce a sensitized cell using an antisense nucleic acid complementary to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60. Although the Examiner concedes that the level of skill in the art is high, he asserts that antisense inhibition is unpredictable, and thus, there is no way to confirm that a selected antisense nucleic acid inhibits proliferation without undue experimentation. Applicants respectfully disagree.

Applicants maintain that the instant patent application provides specific working examples of inhibiting cellular proliferation by providing inhibitory antisense nucleic acids (including SEQ ID NO: 60) that are complementary to at least a portion of a proliferation-

required gene (including *yid*C) as well as extensive guidance which explains a routine method for identifying other inhibitory antisense molecules complementary to a nucleic acid encoding a gene product (YidC) whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence of SEQ ID NO: 60. For example, Applicants describe a method for identifying one or more antisense nucleic acids complementary to a gene which encodes a proliferation-required gene wherein the method also identifies one or more specific inhibitory antisense nucleic acids that are complementary to at least a portion of the proliferation-required gene (see Examples 1 to 3). Once the proliferation-required gene is identified (for example *yid*C), any or all nucleic acids complementary to the gene may then be readily analyzed (see page 38, line 1 to page 40, line 19, including Examples 1 and 2) to identify those that have the ability to inhibit cellular proliferation by reducing the expression of the essential gene product. The types of antisense nucleic acids which can be tested, are specifically described at page 30, lines 11 to 26. Furthermore, at least one embodiment of the instant patent application exemplifies methods of identifying antisense nucleic acids which predictably inhibit proliferation since these antisense nucleic acids are identified by a process that specifically tests their ability to inhibit proliferation (see Examples 1 and 2). Thus, any antisense nucleic acid identified using this process will predictably inhibit proliferation.

In addition to teaching routine methods for identifying inhibitory antisense nucleic acids, Applicants show that increasing the amount of an inhibitory antisense nucleic acid that is expressed inside a cell increases the inhibition of cellular proliferation (see Figure 1 and Example 9). Accordingly, the antisense nucleic acids that are identified function to inhibit proliferation in a dose-dependent manner.

As indicated by the Examiner in his Final Office Action, the level of skill in the art is "very high (the Ph.D. degree with laboratory experience)." Accordingly, a skilled artisan would be able to implement the above-described methods without undue experimentation.

As an illustration of the efficacy of the above-described methods for identifying proliferation inhibiting antisense nucleic acids, the Declaration that is provided herewith describes the identification of a second inhibitory antisense nucleic acid obtained from *E. coli* which is complementary to at least a portion of the *yid*C gene. This second antisense nucleic acid, which was identified using the methods described in Examples 1 and 2 of the instant patent

application, shares no overlap with SEQ ID NO: 60 but has the ability to inhibit *E. coli* proliferation to the same extent as SEQ ID NO: 60.

Another aspect of the enablement rejection relates to the assertion that, given the teachings of the specification, undue experimentation would be required to inhibit the proliferation of all kinds of cells by using an antisense nucleic acid complementary to the gene encoding YidC. Again, Applicants respectfully disagree.

Although the Examiner has acknowledged in the Final Office Action that YidC is conserved across a broad range of species, including bacteria, fungi and plants (see Chen *et al.* as cited in the Final Office Action), to expedite allowance of the pending claims, Applicants have amended Claims 45-50 and 52 to add the limitation that the cell which is sensitized by the expression of the inhibitory antisense nucleic acid is a microbial cell. Furthermore, the claims recite that the antisense nucleic acid is complementary to a nucleic acid in the microbial cell. Applicants' specification clearly enables these claims for the following reasons.

Applicants have provided a working example which demonstrates that the proliferation of *E. coli* is inhibited by expressing an inhibitory level antisense nucleic of SEQ ID NO: 60 inside the cell. As described above and in the accompanying Declaration, Applicants have shown that increasing the expression of the antisense nucleic acid of SEQ ID NO: 60 in *E. coli* increases the inhibition of cell growth, thus causing the cell to become sensitized (see Figure 1, Examples 9 and Declaration). The specification further describes routine computer-based methods for identifying homologs of the *yid*C gene and YidC polypeptide in organisms other than *E. coli* (see page 31, line 9 to page 32, line 20). In addition, the specification describes alternative methods for identifying *yid*C coding sequences in organisms other than *E. coli* by using nucleic acid hybridization (see page 32, line 21 to page 34, line 5). Once a particular *yid*C homolog is identified in a microbe other than *E. coli*, antisense nucleic acids complementary to the *yid*C homolog coding sequence are examined to identify one or more antisense nucleic acids that are capable of inhibiting the expression of the *yid*C gene product thereby inhibiting proliferation. Routine procedures for identifying inhibitory antisense nucleic acids which are complementary to at least a portion of a proliferation-required gene have been discussed above and are thoroughly described at page 38, line 1 to page 40, line 19. Given the high level of skill in the art, the above-described methods can be practiced without undue experimentation.

As a demonstration of the ease and success with which the above-described methods can be implemented, Applicants have identified the YidC homolog in *Staphylococcus aureus* and have shown that antisense nucleic acids capable of inhibiting the expression of the *yid*C gene product inhibit the proliferation of *Staphylococcus aureus*. These experiments, which are described in detail in the Declaration provided herewith, were performed substantially as described in the instant application and were completed without difficulty. In particular, Applicants identified a number of different antisense nucleic acids complementary to the *S. aureus yid*C gene, which when expressed in *S. aureus,* inhibited its proliferation. Results of experiments in which the level of inhibitory antisense expression was varied, indicated that increasing the level of antisense expression increased the inhibition of proliferation (see Declaration).

In view of the current claim amendments, the teachings provided in the specification and the Inventor's Declaration which confirms that inhibitory antisense nucleic acids complementary to *yid*C can be readily obtained without undue experimentation, Applicants maintain that Claims 45-56 are enabled.

The final aspect of the enablement rejection relates to the assertion that, *in vivo* application of antisense techniques is unpredictable, thus, significant trial and error experimentation would be required to determine whether an antisense nucleic acid can function *in vivo*.

Applicants would like to point out that Claims 45-56 are not drawn to a method of treating microbial infections in subjects through the use of antisense therapy. Rather, Claims 45-56 are drawn to a method of identifying a compound which reduces the activity or level of a gene product required for proliferation of a microorganism by expressing an inhibitory antisense nucleic acid that is complementary to at least a portion of the *yid*C gene. The cell is sensitized by expression of the antisense nucleic acid, thereby facilitating identification of compounds which inhibit proliferation. In this light, Applicants submit that no undue experimentation is required to identify and use antisense nucleic acids which have the ability to inhibit microbial proliferation. For example, in several embodiments that are described in the instant application, inhibition of cellular proliferation (cell sensitization) is mediated by introducing into the microbial cell, whose proliferation is to be inhibited, an appropriate expression construct which contains an inhibitory antisense nucleic acid under the control of an inducible promoter (see examples 1, 2, 9 and 12).

Inside the cell, the strength of the antisense-mediated inhibition of proliferation can be modulated by modulating the expression of the inhibitory antisense nucleic acid (see Figure 1 and Declaration). In the instant specification, Applicants have shown that the antisense nucleic acid comprising the nucleotide sequence of SEQ ID NO: 60 predictably and reliably inhibits microbial proliferation when expressed inside the microbial cell. Similarly, the Declaration provided herewith shows that the proliferation of *S. aureus* can be inhibited using any of the antisense nucleic acids identified therein which are complementary to the gene encoding YidC. In view of these facts, Applicants maintain that the specification describes predictable methods for the *in vivo* inhibition of proliferation of a microorganism by expressing an antisense nucleic acid complementary to a gene encoding YidC.

In view of the above remarks and Declaration, Applicants maintain that Claims 45-56 are enabled. Accordingly, Applicants respectfully request that the Examiner withdraw his rejections of Claims 45-56 under 35 U.S.C. § 112, first paragraph.

Withdrawal of Claim 128 and Claim 132

In the Final Office Action mailed on May 12, 2003, the Examiner has withdrawn Claim 128 but has not indicated the status of Claim 132. In particular, the Examiner asserts that amended Claim 128 is drawn to an invention that is different from that which Applicants have elected for examination. Furthermore, the Final Office Action is silent as to the status of Claim 132 which was added in Applicants' response to the Office Action mailed on September 10, 2002 (first Office Action). Applicants respectfully request that the Examiner reconsider his decision to withdraw Claim 128 and consider whether he will examine Claim 132.

Applicants maintain that amended Claim 128 is drawn to elected subject matter. Originally filed Claim 128 is drawn to a method of manufacturing an antibiotic that is identified by any one of several methods recited therein. In particular, originally filed Claim 128 recites: "The method of Claim 127 wherein said screening step comprises performing any one of the methods of Claims 28, 38, 45, 96, 99 and 110." In his Restriction Requirement of July 3, 2002, the Examiner placed Claims 45-56 and 128 together in Group XI. Applicants elected the claims of Group XI for examination. In his first Office Action, the Examiner objected to Claim 128 because it recited several nonelected claims. In response to this objection, Applicants removed all references to nonelected claims from Claim 128. As such, Claim 128 was amended as

follows: "A method for manufacturing an antibiotic comprising the steps of manufacturing a compound which has been determined to inhibit the growth of a sensitized cell using the method of Claim 45." The steps for identifying the compound that is to be manufactured by determining whether it inhibits growth are recited in elected Claim 45, which is duly incorporated into Claim 128. Accordingly, amended Claim 128 is drawn to elected subject matter.

Previously added Claim 132 is also drawn to elected subject matter. In particular, Claim 132 recites, "A method for manufacturing an antibiotic comprising the steps of manufacturing a compound which has been determined to inhibit the growth of a sensitized cell using the method of Claim 46." Claim 46 is a method of identifying compounds which depends from and is in the same group as Claim 45. Thus, the steps for identifying the compound that is to be manufactured by determining whether it inhibits growth are included in Claim 132 by its reference to elected Claim 46. Accordingly, Claim 132 is drawn to elected subject matter.

In view of the foregoing arguments, Applicants respectfully request that the Examiner reinstate claim 128 and enter Claim 132 for examination.

Finality of Office Action

As discussed during the telephonic interview of May 12, 2003, Applicants maintain that the Office Action mailed March 11, 2003 should not have been made final. During the telephonic interview, it was agreed that Applicants would respond to each of the rejections set out in the Final Office Action; however, it was also agreed that the Examiner would reconsider the finality of this Office Action if the claims are not allowed. Applicants believe that the current claim amendments in conjunction with the accompanying remarks and declaration place this case in condition for allowance, and thus, the finality of the Office Action is no longer an issue. However, if the Examiner does not agree that the claims are presently allowable, Applicants respectfully request that the finality of the Office Action be reconsidered as agreed in the telephonic interview.

The Office Action of March 11, 2003, which was the second Office Action on the merits in connection with the instant patent application, was made final because Applicants' claim amendments in response to the first Office Action on the merits allegedly necessitated new grounds for rejection. Applicants would like to point out that the claim amendments did not alter the scope of the claims, and therefore, any claim rejections first appearing in the Final Office

Action did not create a new grounds for rejection. In Applicants' response to the first Office Action on the merits, Claims 45, 52, 55 and 128 were amended and Claim 132 was added. As instructed by the Examiner, Claim 55 was amended to recite a single SEQ ID NO rather than a range of SEQ ID NOs. Claim 52 was reworded to change the phrase "a concentration of inducer" to "an inducer in a concentration." Finally, Claim 45 was amended to recite a single SEQ ID NO and to move language which appeared in the preamble to step (a) of the claim. In the Final Office Action, the Examiner entered the above claim amendments, withdrew Claim 128 and did not examine Claim 132. Because none of the foregoing amendments required the Examiner to search or consider subject matter beyond than that which was encompassed by the originally examined claims, Applicants' claim amendments did not necessitate new grounds for rejection.

In addition to the foregoing, Applicants believe that the Office Action mailed March 11, 2003 should not have been made final since each claim must be examined in view of its broadest reasonable construction. In particular, with respect to questions of written description and enablement (the new grounds for rejection in the Final Office Action), the M.P.E.P. requires that the Examiner first construe the claim given its broadest reasonable interpretation. M.P.E.P. § 2163(II)(A)(1). With respect to elected subject matter (elected SEQ ID NO), the broadest reasonable interpretation of the amended claims was no greater in scope than the broadest reasonable interpretation of the original claims. As such, Applicants maintain that their response to the first Office Action on the merits did not necessitate new grounds for rejection.

In view of the foregoing arguments, Applicants respectfully request that the Examiner withdraw the finality of the Office Action mailed on March 11, 2003.

CONCLUSION

Applicants believe that all outstanding issues in this case have been resolved and that the present claims are in condition for allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is invited to contact the undersigned at the telephone number provided below in order to expedite the resolution of such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: August 8, 2003

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